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(54) Title: METHOD AND COMPOSITION FOR TREATMENT OF ERECTILE DYSFUNCTION

(57) Abstract

The invention relates to the treatment of impotence or erectile dysfunction by using prostaglandins that are selective EP_2 or EP_4 prostanoid receptor agonists. The prostaglandin medicaments can be formulated for intracavernous injection, or for transurethral or transdermal application.

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METHOD AND COMPOSITION FOR TREATMENT OF ERECTILE DYSFUNCTION

Field of the invention

The present invention relates to the treatment of impotence or erectile dysfunction, and more particularly to a novel prostaglandin based composition therefore and the use thereof for treating impotence or erectile dysfunction.

Background of the invention

Erectile dysfunction is a disorder characterized by the inability of the male to develop and maintain erection for satisfactory sexual intercourse. Erectile dysfunction is a frequent disorder particularly amongst elderly men which may lead to reduced quality of life and psychological problems. It is estimated that there may be as many as 10-20 million people in the United States suffering from erectile dysfunction, and an estimated 30 million males with at least partial erectile dysfunction (NIH Consensus Conference 1993). The prevalence of erectile dysfunction has been reported to be about 5% at age 40, and up to 25% at age 65 or older. Thus erectile dysfunction is a major clinical challenge of increasing importance with the increased standard of living and demand of a better quality of life.

The ethiology of erectile dysfunction may be psychogenic or organic. The latter seems to account for the majority of cases. Such organic causes include vascular, endocrinological, and neurological diseases as well as trauma. Patients suffering from diabetes are typically at risk. While in many cases erectile dysfunction caused by psychogenic factors may be reversible, impotence caused by organic factors needs adequate therapy. Such therapy comprises surgical intervention, devices and medical treatment. With more effective and better tolerated drugs there is a clear tendency towards medical therapy in the treatment of erectile dysfunction.

The main modalities of medical therapy consist of systemic medication, usually peroral, and local medication in the genitourinary tract. Typical drugs given orally include e.g. yohimbine, an alpha-2 adrenergic antagonist, and testosterone, the male sex hormone. Furthermore bromocriptine has also been used, as well as antiserotoninergic agents such as trazodone, ketanserin and mianserin. Recently, a selective type 5-phosphodiesterase inhibitor sildenafil (Viagra™) has been approved for clinical use. In addition there are many other drugs that have been tested and used for the treatment of erectile dysfunction. Drugs given locally include e.g. papaverine, a smooth muscle relaxing agent, and phentolamine, an alpha-adrenergic antagonist as well as prostaglandins, particularly prostaglandin E_1 (PGE_1; alprostadil).These drugs relax smooth muscle, thus promoting the development of erection, and are given by local injection into the cavernous tissue of the penis. Formulations for intraurethral (transurethral) administration of prostaglandins have also been developed (Wolfson et al., 1993; Bradley et al., 1996) and are described in several patents and patent applications, for instance in WO 93/00894, WO 91/16021 and EP-A-357581.

It is a clear advantage to administer the drug locally into the diseased or dysfunctional organ since a better effect is achieved, and usually less systemic side-effects are induced. However, the local side-effects, mainly pain and priapism, may constitute a problem. The latter meaning prolonged erection which potentially can lead to necrosis and irreversible damage to the reproductive organ has been minimized by the use of prostaglandins, above all PGE_1. However, PGE_1 given by intracavernous injection or transurethrally causes local pain in as many as 10-30% of the patients. In a recently published study transurethral administration of PGE_1 resulted in pain sensation in about 35% of the patients, and 11% of the patients reported pain after every treatment with alprostadil (Padma-Nathan et al., 1997). It is thus obvious that local pain constitutes one of the most significant side-effects of PGE_1, and prostaglandin analogues without pain inducing effect would be desirable for clinical use.

Summary of the invention

We have now unexpectedly found that certain prostaglandin analogues of the E-type, more specifically agonists of the EP_2 prostanoid receptor, exert good relaxant effect in

the penile cavernous tissue, and in blood vessels while exhibiting markedly reduced pain inducing effect. In particular we have found that PGE_2 analogues substituted in carbon 18, 19 or 20 with hydroxyl (OH) exert beneficial effects, and especially one analogue, namely 19R-OH-PGE_2, exhibited a surprisingly advantageous effect with respect to relaxation of penile cavernous tissue and blood vessels without inducing pain as studied in an animal model.

Thus, in a first aspect, the present invention provides a composition for the treatment of impotence or erectile dysfunction, comprising a prostaglandin which is a selective EP_2 or EP_4 receptor agonist, or an active derivative including the free acid, a salt or an ester thereof, optionally together with a physiologically acceptable carrier or vehicle.

In a second aspect, the invention provides a method of treating impotence or erectile dysfunction, which method comprises administering a therapeutically active and physiologically acceptable amount of the composition to an individual in need thereof.

In a third aspect, the invention provides the use of a selective EP_2 or EP_4 receptor agonist, or an active derivative including the free acid, a salt or an ester thereof, for the preparation of a medicament for the treatment of impotence or erectile dysfunction.

In still another aspect, the invention provides a method for eliminating or at least considerably reducing side effects, such as pain and irritation, observed in connection with the use of prostaglandin derivatives for treatment of impotence.

Brief description of the Figures

Fig. 1 is a diagram showing the concentration-response relation for PGE_1 and 19R-hydroxy-PGE_2 in isolated preparation of human corpus cavernosum precontracted with 10^{-6} M norepinephrine.

Fig. 2 is a diagram showing the vasodilatory effect of PGE_1 and and 19R-hydroxy-PGE_2 on rabbit penile blood vessels precontracted with 10^{-6} M norepinephrine

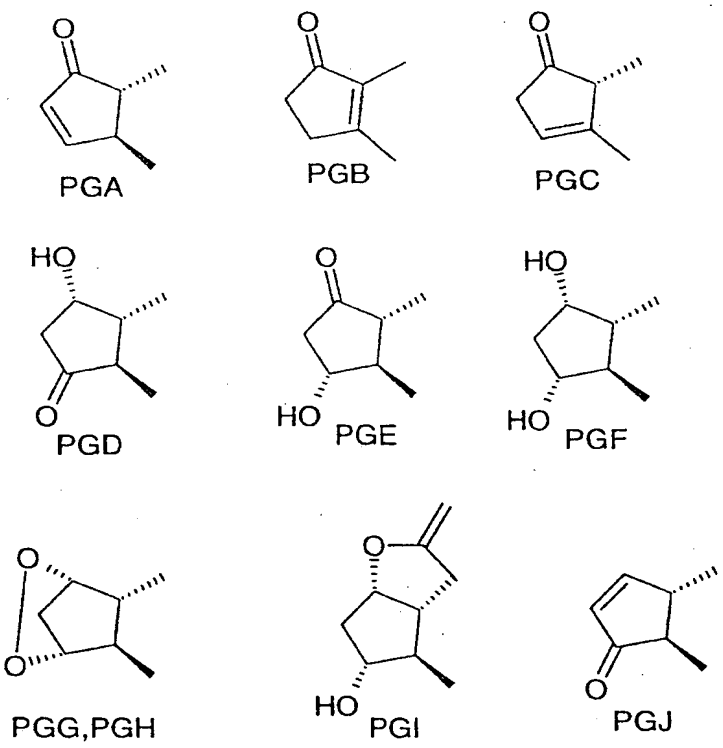
Detailed description of the invention

Penile erection is based on three main physiological events: an increase in the arterial blood flow, a relaxation of the expansive tissue of the corpora cavernosa and the corpus spongiosum, and an obstruction of the venous return by mechanical compression of the veins caused by the expansive tissue. PGE_1 and the EP_2 receptor agonists cause vasodilatation and relax the expansive tissue to about the same extent, and thus promote the development of erection. However, PGE_1 being a natural prostaglandin with low selectivity for specific prostanoid receptors has a marked irritant effect and causes pain as evident in clinical trials performed with alprostadil (e.g. Padha-Natham, 1997) and as will also be shown in the experimental part further below.

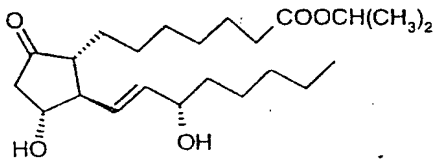
According to the invention, however, prostaglandin analogues with selectivity primarily for the EP_2 receptor which induce the same beneficial effect but with significantly less irritant effect are much more preferable as it can be predicted that such analogues will cause no or only minimal pain in clinical practice. To facilitate the understanding of the invention, a general description of prostaglandins is first given.

The prostaglandins are fatty acids usually derived from the precursors eicosatrienoic, eicosatetraenoic or eicosapentanoic acid through metabolic steps involving oxygenation. The prostaglandins typically carry a cyclopentane ring to which two carbon chains link, the upper chain usually being called the alpha chain and the lower chain the omega chain. The alpha chain is a 7 carbon chain with a terminal carboxylic acid moiety whereas the omega chain is an 8 carbon methyl-terminated aliphatic chain. Depending on the number of double bonds in these chains subscripts of 1 to 3 are used. In prostaglandins with subscript 1, e.g. PGE_1, the double bond is situated between carbons 13 and 14 in the omega chain, and it exhibits trans configuration in naturally occuring prostaglandins. In prostaglandins with subscript 2, e.g. PGE_2, an

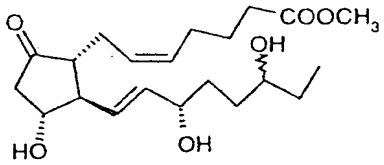
additional double bond in the cis configuration exists between carbons 5 and 6 in the alpha chain, and finally in prostaglandins with subscript 3 a third double bond is situated between carbons 17 and 18 in the omega chain. This double bond also exhibits cis configuration in naturally occuring prostaglandins. All naturally occuring prostaglandins carry a hydroxyl group in carbon 15, which is essential for biological activity. The substituents and the configuration of the cyclopentane ring determine whether the prostaglandin is of the A, B, C, D, E, F, G, H, I or J type as depicted in Scheme 1 below. The prostaglandins that have been used to exemplify the present invention are of the E-type, and the chemical structures of these prostanoids are depicted in Scheme 2. Except for 18RS-OH-PGE_2-methyl ester the prostaglandin analogues were also used as acids.



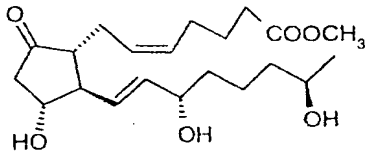
Scheme 1



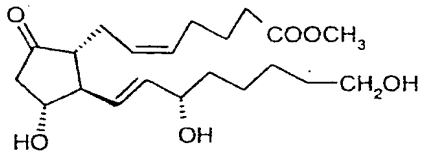
PGE1-Isopropyl ester



18RS-Hydroxy-PGE2-methyl ester



19R-Hydroxy-PGE2-methyl ester



20-Hydroxy-PGE2-methyl ester

Scheme 2

The prostaglandins exert their pharmacologic effect through specific G protein coupled membrane receptors. There are at least 8 different receptors for the endogenous prostaglandins, namely the FP ($PGF_{2\alpha}$), EP_1, EP_2, EP_3, EP_4 (PGE_2), DP (PGD_2), IP (PGI_2), and TP (TxA_2) receptors, the most common naturally occuring ligand for respective receptor being shown within parentheses. At least for the EP_3 receptor splice variants have been shown to exist. The EP_2 and EP_4 receptors are closely related, and probably mediate similar effects. We have therefore studied the effect only on the EP_2 receptor, and regard it to represent the EP_4 receptors as well in the case the compounds studied would have an effect on that receptor, too. The

molecular biology and pharmacology of the prostanoid receptors have recently been reviewed by Coleman et al., 1994.

From a therapeutic point of view a problem with the endogenous prostaglandins is that they exert effects on many different prostanoid receptors. Each endogenous prostaglandin has a preference for one specific receptor type, but is not very selective and usually distinguishes poorly between the receptor subtypes, i.e. the EP receptors. Thus PGE_1 and PGE_2 are good ligands for all subtypes of the EP receptor. Consequently selective effects on one of the subtypes of the EP receptor is impossible to achieve with the endogenous prostaglandins. However, certain synthetic prostaglandin analogues, e.g. butaprost, 11-deoxy-PGE_1 and AH13205 as well as a naturally occuring metabolite of PGE_2, namely 19R-OH-PGE_2, are selective EP_2 prostanoid receptor agonists.

18-OH-PGE_2, 19R-OH-PGE_2 and 20-OH-PGE_2 are effective EP_2 receptor agonists with selectivity for the EP_2 receptor over the EP_3 receptor. The endogenous PGE_1 is unselective and does not distinguish between the EP receptor subtypes sufficiently, and furthermore significantly spills over on the DP/IP receptors which e.g. the 18-, 19- and 20-OH substituted PGE_2 analogues do not. However, PGE_1 has been included as a reference substance as it is the only prostaglandin currently in clinical use for the treatment of erectile dysfunction.

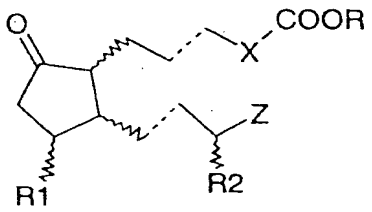
Accordingly, high selectivity or specificity to the EP_2 receptor compared to other prostaglandin receptors, particularly the EP_3 receptor, characterizes the compounds to be used in the method or compositions according to the present invention. It need not be said that the more specific the compound is for the EP_2 receptor the better results are obtained, but a certain advantage is, of course, achieved also in cases of some interaction with other receptors. High selectivity in this connection means that the effect on the EP_2 receptor is at least more than 5 times, especially more than 10 times, and in particular more than 100 or 1000 times the effect on other prostaglandin receptors.

As stated above, according to the present invention, in particular the selective EP_2 receptor agonist 19R-OH-PGE_2 and its carboxylic acid esters appear to be unique and ideally suited for the treatment of erectile dysfunction. In this context it should be mentioned that 19R-OH-PGE_2 is a metabolite of PGE_2 in the genital tract, and can be found in large quantities normally in human semen (Taylor and Kelly, 1974). However, the physiological role of this unique metabolite is unknown. Thus, 19R-OH-PGE_2 and its carboxylic acid esters constitute a very attractive alternative to PGE_1 as medication for impotence since this analogue causes no pain, is as effective as PGE_1, and furthermore occurs normally in the body.

With respect to 19R-OH-PGE_2 which appears ideally suited for treatment of erectile dysfunction, it should be observed that various modifications or substitutions of the molecule are possible as long as the new derivatives exhibit selective agonism on the EP_2 receptor.

In Formula I, the wavy bonds represent the α (S) or β (R) configuration, and the dashed bonds represent a single, a triple or a double bond in the cis or trans configuration. R in the formula is hydrogen, a salt moiety, e.g. an alkali or ammonium salt, a straight or branched saturated or unsaturated alkyl group, preferably with 1-10 carbons, an alicyclic ring, preferably with 3-8 carbons, arylalkyl, preferably aryl-C_{2-5} alkyl, or an aryl ring. X is a straight chain, saturated or unsaturated, preferably consisting of 2-5 carbons optionally interrupted by a heteroatom (O, S, N), and the chain may contain an alicyclic ring, preferably C3-C7 cycloalkyl, or an aryl or heteroaryl ring. R1 and R2, which are identical or different, are hydrogen, hydroxy, halogen, oxygen (=O or alkoxy) or an alkyl group with 1-3 carbons or analkoxy group with 1-3 carbons or an ester OCOR3, where R3 is a straight or branched, saturated or unsaturated alkyl group preferably containing 1-10, especially 1-6 carbons, or a cycloalkyl, preferably containing 3-7 carbons, or an aryl or arylalkyl group, preferably aryl-C_{2-5} alkyl (e.g. benzyl). Optionally C10 can be substituted e.g. to contain a mono- or dialkyl group.

Z is an alkyl chain of 1-8, e.g. 3-8 and 2-4 carbons, saturated or unsaturated, optionally interrupted by one or more heteroatoms (O, S, N), and containing one or more, preferably one substituent Y, attached to a carbon atom within the chain or a carbon atom in terminal position. The chain Z may be branched, containing alkyl (preferably methyl) substituents and/or contain an alicyclic ring, e.g. a cycloalkyl, or an aryl (esp. a benzene) or heteroaryl ring, in inter- or terminal position. Y, is hydroxy, sulfhydryl, amino, methylamino, dimethylamino, C_{1-3} alkoxy or halogen (Cl, Br, F) or oxygen (keto). In a preferred embodiment of the invention Y is attached to carbon 18, 19 or 20. In the most preferred embodiment Y is OH and attached to carbon 19. At present it is believed that the inventive concept is based on the electronegative effect introduced by Y.



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The prostaglandins may be epimeric mixtures as well as in the form of the individual epimers.

Description of suitable embodiments

The EP_2 prostanoid receptor agonists according to the present invention can be used as the normal carboxylic acids, salts (e.g. cationic) or as ester prodrugs, preferentially carboxylic acid alkyl esters. The active compounds can either be administered by intracavernous injection, transurethral, or transdermal application (including on the glans of the penis) in a pharmaceutically acceptable delivery medium. For intracavernous injection sterile isotonic water based solutions are preferred. These should be buffered and have a pH of around 7.0-7.5 or at least in the interval of 6.0-8.0. For solubilisation of the prostaglandin different micellar systems can be used such as polysorbate. Cyclodextrins may also be employed for solubilisation. If the

prostaglandin analogues to be used are unstable in water solution the compounds may be lyophilized and dissolved immediatly before use or stabilized with different stabilizing agents such as cyclodextrins. Different slow-release formulations adapted to the requirements of injectable solutions may also be employed. If the new medicament is to be administered transurethrally the active principle may be formulated in creams, gels or ointments, suppositories, or other solid state forms. Furthermore a device (applicator) for introducing the medicament into the urethra is also needed. It is understood that such a device can be designed in a variety of ways and consist of different materials. If the new medicament is to be administered transdermally various forms of creams, ointments, gels, and slow release systems such as patches may be employed. Also the inner surface of condoms or bandages may be lined by a suitable formulation containing the new medicament. Gels, creams, ointments, and different solid state formulations may or may not contain preservative such as benzalkonium chloride, chlorhexidine, thiomersal, parabenzoic acid, and other compounds with satisfactory antimicrobial effect. For intracavernous injection the dose interval is 0.001-1 mg, typically 0.01-0.1 mg per injection. For transurethral and transdermal administration the dose interval is 0.01-10 mg, typically 0.1-1 mg for transurethral administration, and 0.1-10 mg for transdermal administration.

Accordingly the new medicament should be administered locally to the penis either by injection, or by applying it into the urethra with an applicator or syringe, or it should be applied topically on the skin or the mucous membrane of the penis. Such treatment should be initiated typically 5-60 min, depending on the mode of administration, before intercourse.

Exemplification of the invention

PGE_1 was obtained from Chinoin, Pharmaceutical and Chemical Works Co. Ltd., Budapest, Hungary.

DBU (644 mg, 4.2 mmol) in acetonitrile (1ml) was added dropwise to a stirred solution of PGE_1 (300 mg, 0.84 mmol) in acetonitrile (3ml) at 0 °C. The mixture was allowed to warm to room temperature whereupon isopropyl iodide (1142 mg,

6.72 mmol) in acetonitrile (2ml) was added dropwise. After being stirred for 10h (TLC monitoring), the reaction mixture was quenched with water (8ml), the mixture was extracted with ethyl acetate (2x50ml), and the extract was washed with brine (10ml), citric acid 3% (10ml), and finally sodium hydrogen carbonate 5% (2x10ml). After drying with anhydrous sodium sulphate, the solvent was removed in vacuo and the residual oil was chromatographed on silicagel using ethyl acetate as eluent. This afforded 230 mg of the product (69%) of the title compound as a colorless oil: R_f = 0.18 (ethyl acetate); ^{1}H NMR (CDCl3) δ 0.89 (m, 3H), 1.2 (d, 6H), 1.21-1.4 (m, 10H), 1.42-1.62 (dm, 6H), 2.2-2.4 (dm, 4H), 2.7-2.75 (dd, 1H), 4.0-4.17 (dm, 2H), 5.0 (m, 1H), 5.5-5.7 (dm, 2H).

Synthesis of 18RS-hydroxy-PGE_2-methyl ester

1. Preparation of Dimethyl-(2-oxo-5-heptyne)-phosphonate.(2)

To a stirred suspension of dry sodium hydride (3.13 g, 124,07 mmol) in dry THF (100 ml) at room temperature was added dropwise a solution of dimethyl-(2-oxopropyl)-phosphonate (20,61 g, 124,07 mmol) in dry THF (50 ml) under N_2. The reaction mixture was stirred for 1h, then cooled in an ice-bath and treated with a solution of n-butyllittium (7.95 g, 124, 07 mmol) in hexane, causing a dark brown solution to be formed . Stirring was continued for 1 h at 0 °C, followed by dropwise addition of 1-bromo-2-butyne.1 (15 g, 112,79 mmol) in THF (30 ml). The reaction mixture was gradually warmed to room temperature and after 1 h (TLC monitoring) the reaction mixture was quenched with ice-water, HCl 1M to pH about 4 and extracted, twice, with ethyl acetate. The organic layer was washed with brine and chromatographed on silica gel using EtOAc as eluent. Rf=0.38 (silica gel, ethylacetate), yield 18g (73%).

2. (1S,5R,6R,7R)-6-Formuyl-7-{(4-phenylbenzoyl)oxy}-2-oxabicyclo {3.3.0}octan-3-one.(3)

A mixture of Coreys lactone (23,06 g, 65,44 mmol)), DCC (40,50 g, 196,31 mmol)), DMSO (27,8 ml, 392,6 mmol) and phosphoric acid 85% (2,2 ml) in DME (130 ml) was stirred at room temperature for 2h (TLC monitoring). The precipitate was removed on silica-gel pad washed with DME (2 x 50 ml). The filtrate was concentrated in vacuo and used for the next step without isolation.

4. (1S,5R,6R,7R)-6-(3-Oxo-6-yn-1E-1-octenyl)-7-{(4-phenylbenzoyl)oxy}-2-oxabicyclo{3.3.0}octan-3-one.(4)

To a stirred suspension of sodium hydride (1,98 g, 78,53 mmol)) in DME (140 ml) under N_2 was added dropwise the above phosphonate 2 (18,56 g, 85,07 mmol) and stirred mechanically at room temperature for 1,5 h. The mixture was then cooled to -5 °C, and a solution of the above crude Coreys aldehyde 3 was added dropwise. After 30 min at 0 °C and 2 h at room temperature (TLC monitoring), the reaction mixture was neutralised with citric acid 5% and extraced with ethyl acetate (2x100ml). The organic layer was dried and evaporated. The residue (oil) was chromatographed on silica-gel using ethyl acetate and 10% methanol in ethyl acetate successively , giving a light yellowish oil. R_f = 0.58(silica-gel, ethyl acetate), yield 52%.

5. (1S,5R,6R,7R)-6-(3,6-Dioxo-1E-1-octenyl)-7-{(4-phenylbenzoyl)oxy}-2-xabicyclo{3.3.0}octan-3-one.(5)

To the acetylenic solution 4 in acetonitrile:water 2:1 (100 ml) was added mercuric oxide (13,8 g, 63,73 mmol)) and sulfuric acid 1M (25,49 ml, 25,49 mmol)). The reaction mixture was stirred magnetically. After about 1 h at room temperature (TLC monitoring) the reaction mixture was worked-up by addition of ethylacetate and HCl 1M. The organic layer was dried and evaporated. The crude oil was used for the next step without purification. R_f = 0.44 (silicagel, EtOAc), yield = 41%.

6. (1S,5R,6R,7R)-6-(3RS,6RS-Dihydroxy-1E-1-octenyl)-7-{(4-phenylbenzoyl) oxy}-2-oxabicyclo{3.3.0}octan-3-one.(6)

To a stirred solution of the above diketone 5 (12,0 g, 26.1 mmol) and cerium chloride hepta hydrate (5.83 g, 15,64 mmol) at -20 °C in methanol: methylene chlorider 1:1 was added sodium borohydride (1.48 g, 39,09 mmol)) in small portions under N_2. After 30 min (TLC monitoring). The reaction mixture was quenched with HCl 1M to pH about 4-5,and diluted with water (50 ml) and ethyl acetate (100 ml). The organic layer was separated and the water layer was washed twice with EtOAc, dried and evaporated The residue was purified on silica gel using EtOAc as eluent. The title

compound 6 was obtained as colorless oil: yield 8.8 g (71%). R_f = 0,15, 0,13 corresponding to the two isomers 15α and 15β (silicagel, EtOAc).
^{1}H NMR ($CDCl_3$) δ 0,9 (m, 3H), 1,4-1,8 (dm, 6H), 2,3 (d, 1H), 2,5-2,9 (dm, 5H), 3,5 (m, 1H), 4,2 (m, 1H). 5.1 (m, 1H), 5,3 (m, 1H), 5,7 (m, 2H), 7,4 (m, 1H), 7,5 (m, 2H), 7,6-7,7 (dd, 4H), 8,1 (d, 2H); ^{13}C NMR ($CDCL_3$) d 176,40 (C6H4C=O), 16591 (lactone C=O), 146,07, 139,83, 136,21, 130,15, 128,91, 128,31, 127,15, 83,27, 79,13, 73,11, 71,79, 71,48, 54,08, 42,84, 42,75, 37,55, 34,85, 34,01, 33,43, 32,95, 32,09, 30,17, 9,96.

7. (1S,5R,6R,7R)-6-(3RS,6RS-Di t butyldimethylsilyloxy-1E-1-octenyl)-7-{(4-phenylbenzoyl)oxy}-2-oxabicyclo{3.3.0}octan-3-one.(7)

To a stirred solution of the above dihydroxy compound 6 (8,6 g, 18,51 mmol) in dichloromethane was added triethyl amine (12,83 ml, 92,56 mmol)), t-butyldimethylsilyl chloride (13,95 g, 92,56 mmol)) and 4-dimethylamino pyridine (1,13 g, 9,26 mmol). The mixture was stirred magnetically for 15 h at room temperature. The reaction mixture was diluted with ether, filtered and the precipitate was washed with ether. The organic layer was washed with brine, dried and concentrated in vacuo. The residue was chromatographed on silica gel using 5% ether in dichloromethane. R_f = 0.58 (silica gel, 5% ether in CH2Cl2).Yield 12,2 g (92%)

8. (1S,5R,6R,7R)-6-(3RS,6RS-Di t butyldimethylsilyloxy-1E-1-octenyl)-7-{(4-hydroxy}-2-oxabicyclo{3.3.0}octan-3-one.(8)

To a stirred solution of the above disilyl ether 7 (12 g, 17,31 mmol) in methanol was added potassium carbonate (1,2 g, 8,66 mmol). The reaction mixture was stirred at room temperature for 4 h (TLC monitoring). The mixture was neutralised with citric acid 5%, extracted twice with ethyl acetate (100 ml), dried and concentrated in vacuo. The oil was chromatographed on silica gel using gradient elution with 5% ether in CH_2Cl_2 and EtOAc:acetone 1:1 successively. R_f = 0.43 (silica gel, ethyl acetate), yield = 8,86 g (74%)

9. (1S,5R,6R,7R)-6-(3RS,6RS-Di t butyldimethylsilyloxy-1E-1-octenyl)-7-{(4-t-butyldimethylsilyloxy}-2-oxabicyclo{3.3.0}octan-3-one.(9)

To a stirred solution of the above dislyloxy ether 8 (6,6 g, 12,86 mmol) in CH_2Cl_2 at room temperature was added triethyl amine (7,14 ml, 51,47 mmol) t-butyldimethyl-silyl chloride (7,76 g, 51,47 mmol) and 4-dimethyl aminopyridine (0.47 g, 3,9 mmol). The reaction mixture was worked-up as in 7. The crude product was chromatographed on silica gel using 5% ether in dichloromethane to give a pure trisilyloxy ether product 9 as an oil. $R_f = 0.62$ (silica gel, 5% ether in CH_2Cl_2), yield 7,8 g, (96%)

10. (1S,5R,6R,7R)-6-(3RS,6RS-Di t butyldimethylsilyloxy-1E-1-octenyl)-7-{(4-t-butyldimethylsilyloxy}-2-oxabicyclo{3.3.0}octan-3-ol.(10)

A solution of diisobutyl aluminium hydride (DIBAL-H) (2,9 g, 20,87 mmol) in dry THF was added dropwise to a stirred solution of the above trisilyl ether lactone 9 (7,7 g, 12,24mmol) in THF (80 ml) at -72/-80 °C. After 1h (TLC monitoring), the reaction mixture was quenched with ice (15 g) and ethyl acetate (150 ml), filtered and the filtrate was concentrated in vacuo. The residue was used directly without separation in the next step. $R_f = 0.27$ (Silica gel, 5% ether in dichloromethane).

11. 11,15RS,18RS-Tri-t-butyldimethylsilyloxy-$PGF_{2\alpha}$ (11)

To a stirred suspension of 4-carboxybutyl-triphenylphosphonium bromide (21,70 g, 48,95 mmol) in dry THF under N_2 at -5 °C was added potassium tert-butoxide (10,99 g, 97,91 mmol) and the mixture was stirred at room temperature for 30 min. To the resultant red-orange solution of ylide at -15/-10 °C was added the lactol 10 (7,7 g, 12,24 mmol) in THF, and the mixture was stirred for 2-3 h (TLC monitoring) at room temperature. The reaction mixture was diluted with water and quenched with citric acid 15 % to pH 6-7 and extracted with EtOAc, dried and concentrated in vacuo. The resultant slurry was used directly without isolation for the next step.

12. 11,15,18RS-Tri-t-butyldimethylsilyloxy-$PGF_{2\alpha}$ methyl ester (12)

Methyl iodide (8,6 g, 61,20 mmol), was added to a stirred solution of the crude product 10 (8,73 g, 12,24 mmol) and N,N-Diisopropyl ethyl amine (9.473 g, 73,44 mmol) in acetonitrile at room temperature. After 15h (TLC monitoring) the mixture was diluted with water (100 ml) and ethyl acetate (150 ml), washed with sodium hydrogen carbonate 5% (60 ml) and brine (70 ml). The organic layer was dried and

evaporated in vacuo. The residue was chromatographed on silica gel using EtOAc as eluent. $R_f = 0.18$ (silica gel, EtOAc:hexane 1:9).

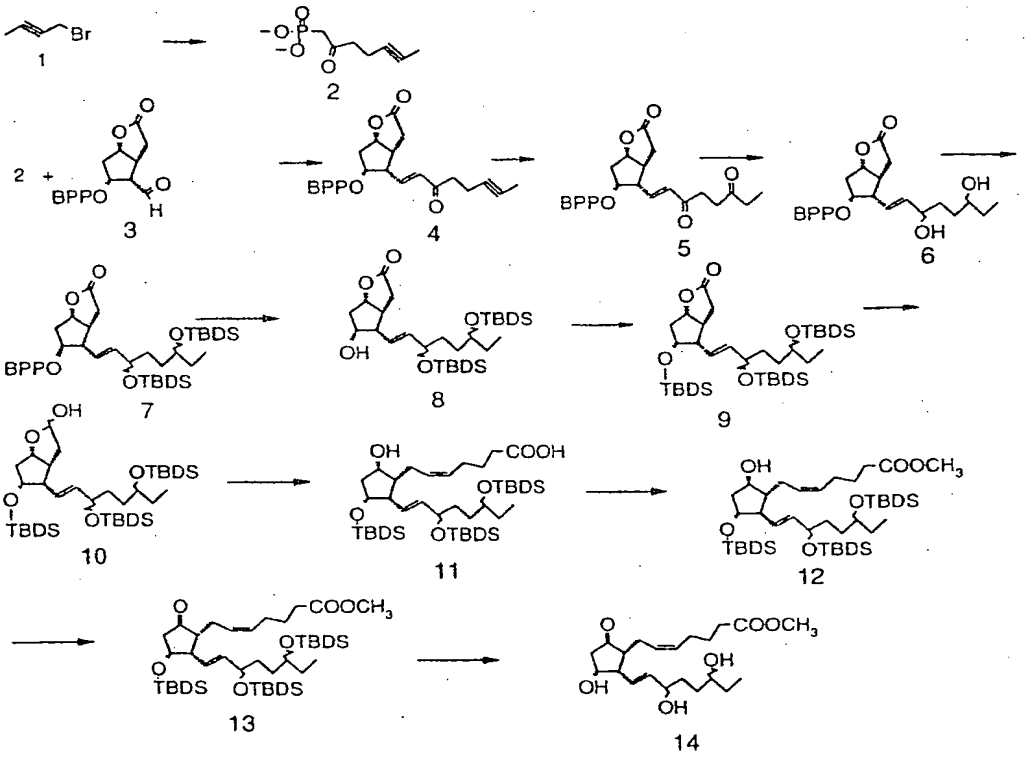
13. 11,15,18RS-Tri-t-butyldimethylsilyloxy-PGE_2 methyl ester (13)

To a stirred solution of the compound 11 (3,3 g, 4,54 mmol) in dichloromethanne was added pyridinium chlorchromate (PCC).(3,9 g, 18,15 mmol) treated with aluminium oxide (1g PCC was stirred with 5g aluminium oxide in acetone, the solvent was removed in vacuo giving a light yellow powder). The resulting suspension was stirred at room temperature for 4h (TLC monitoring). The suspension was filtered on silica gel pad, washed with dichloromethane. The solvent was removed and the resulting oil was diluted with ether and washed with water (50 ml), sodium hydrogen carbonate 5% (50 ml). The solvent was removed in vacuo. The residue was chromatographed on silica gel using 5% ether in CH_2Cl_2. $R_f = 0.32$ (silica gel, EtOAc:hexane 1:9), yield 3,1 g (86%)

14. 18RS-hydroxy PGE_2 methyl ester (14)

The protecting groups 11,15,18-tri-t-butyldimethylsilyl chloride were removed by addition of HF 4% (108 ml) to a solution of 13 (3,0 g, 3,98 mmol) in acetonitrile (300 ml). The reaction mixture was stirred at room temperature for about 8h (TLC monitoring). The reaction mixture was worked-up by addition of EtOAc (200 ml). The organic layer was separated and washed with sodium bicarbonate 5% and the pH was adjusted to about 6. The organic layer was washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel using gradient elution with CH_2Cl_2, EtOAc and 5-10% methanol in ether successively (The stationary phase, silica gel, in the column must be washed with the eluent containing triethylamine before purification, to avoid isomerization) 18RS-hydroxy-15S-PGE_2 Me ester $R_f = 0.16$ (5% MeOH in ether); yield 310 mg.
18RS-hydroxy-15R-PGE_2 Me ester $R_f = 0.20$ (5% MeOH in ether);
yield 248 mg.
18RS-hydroxy-PGE_2 methyl ester 1H NMR (CDCl3) δ 0,9 (t, 3H), 1,4-1.7 (dm, 8H), 2,1 (m, 2H), 2,2 (m, 2H), 2,3-2,4 (m, 5H), 2,7 (m, 1H), 3,6 (m, 1H, 18-C*H*OH), 3,7 (s, 3H), 4,05, (m, 1H, 15-C*H*OH), 4,2 (m, 1H, 11-C*H*OH), 5,3-5,5 (dm, 2H, db), 5,6-5,8 (dm, 2H, db);

13C (NMR) δ 214, 174,24, 136,7, 131,3, 130,8,126,5, 72,36, 71,78, 71,70, 55,54, 54,54, 53,70, 51,60, 46,06, 34,06, 33,42, 33,00, 32,10, 30,34, 30,29, 30,07.



Scheme 3

Synthesis of 19-R-hydroxy-prostaglandin E_2-methyl ester

19R-hydroxy-prostaglandin E_2 was obtained from Cayman Chemicals, Ann Arbor, Michigan, USA. Methyl iodide (9.2 mg, 0.065 mmol) in acetonitrile (1.0 ml) was added drop-wise to a stirred solution of 19R-hydroxy-prostaglandin E_2 (4 mg, 0.011 mmol), and N,N-diisopropyl ethyl amine (7 mg, 0.054 mmol) in acetonitrile. More methyl iodide (4.5 mg, 0.032 mmol) in acetonitrile was added after 6 h and the stirring was continued for 12 h (TLC monitoring). The reaction mixture was quenched with water (5.0 ml) and extracted with ethyl acetate (2x10 ml), and the organic phase was washed with sodium hydrogen carbonate 5% (5 ml) and hydrochloric acid 0.5M (5 ml). After drying with anhydrous sodium sulphate, the solvent was removed in vacuo and the residue was chromatographed

on silica-gel using ethyl acetate: acetone 1:1 and acetone as eluent. This afforded 3.2 mg (72.7%) of the product as a colorless oil: R_f=0.17 (ethyl acetate:acetone:acetic acid 1:1:0.01) ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H), 1.5-1.7 (m, 8H), 2.1-2.6 (mm, 9H), 3.7 (s, 3H), 3.8 (m, 1H), 4.1 (m, 1H), 4.2 (m, 1H), 5.3-5.5 (dm, 2H), 5.6-5.8 (dm, 2H).

Synthesis of 20-OH-prostaglandin E_2-methyl ester

The commercially available 20-hydroxy PGE_2 (Cayman Chemicals, Ann Arbor, Michigan) (2.0 mg, 0.0054mmol) was esterified in acetonitrile (2,0 ml) with methyl iodide (4.6 mg, 0.0327 mmol) in the presence of N,N-diisopropyl ethylamine (3.5 mg, 0.027mmol). The reaction mixture was stirred at room temperature for 10 h (TLC monitoring, silica gel, ethyl acetate). The reaction mixture was quenched with water (3,0 ml) and extracted with ethyl acetate (2x10 ml). The organic layer was dried and concentrated in vacuo and the residual oil was chromatographed on silica gel using ethyl acetate:acetone 1:0.5 as eluent; R_f = 0.38(silica gel, ethyl acetate:acetone 1:1).

PGE_1-isopropyl ester, 18RS-hydroxy-PGE_2-methyl ester, 19R-hydroxy-PGE_2-methyl ester and 20-hydroxy-PGE_2-methyl ester were dissolved in 0.5 % polysorbate-80 as a stock solution, and were diluted in 0.5% polysorbate-80 to the appropriate concentrations.

Pharmacological experiments

Human penile cavernous tissue was obtained fresh from surgery, and representative tissue samples were mounted in smooth muscle tissue baths containing a modified Kreb's solution consisting of NaCl 119 mM, KCl 4.6 mM, $MgCl_2$ 1.2 mM, NaH_2PO_4 1.2 mM, $NaHCO_3$ 15 mM, $CaCl_2$ 1.5 mM and glucose 11 mM. The solution also contained indomethacin at a final concentration of about 3 μM. The solution was continuously bubbled by 95% O_2 and 5% CO_2, and the temperature was kept at 37 °C.

The tissue preparations were stretched by a force corresponding to 500 mg, and were given a contractile tone by the addition of norepinephrine at a concentration of 10^{-6} M. Concentration-response curves were then constructed by adding cumulatively increasing concentrations of the prostaglandin analogues to the bath in a routine way. The relaxant effect was normalized by comparing to that of carbachol in the same preparation. PGE_1 and 19R-OH-PGE_2, respectively, were used as acids.

To study the effect of the PGE_1 and 19R-OH-PGE_2 on the penile vasculature, penile blood vessels of the rabbit were isolated and mounted as ring segments in a small vessel myograph (J.P. Trading, Denmark) containing a solution consisting of NaCl 119 mM, KCl 4.7 mM, $CaCl_2$ 1.5 mM, $MgSO_4$ 1.17 mM, KH_2PO_4 1.18 mM, $NaHCO_3$ 25 mM, EDTA 0.027 mM and glucose 11 mM. The solution also contained indomethacin at a final concentration of about 3 µM, and was continuously bubbled by 95% O_2 and 5%CO_2. The temperature was kept constant at 37 °C. The vessels were stretched and then precontracted using 10^{-6} M norepinephrine, and the vasorelaxant effect of the prostaglandin analogues was normalized by comparing it to that of papaverine in the same preparation. Cumulative concentration-response curves were constructed for the analogues.

The vasodilatory effect of the prostaglandin analogues was also studied in the rat by registering the blood pressure reducing effect. This is a relevant in vitro model for showing general vasodilatory effect of importance for inducing erection since vasodilation in penis is needed for achieving erection. Rats were anaesthetized with a mixture of ketamine and xylazin and the prostaglandin analogues were infused intravenously. The blood pressure was continuously registered in a femoral artery. Each analogue was infused in 3 escalating doses in the same animal. None of the compounds was found to have any significant effect of the heart rate and the immediate reduction in arterial blood pressure therefore reflects an acute vasodilatory response to the prostaglandin analogues tested. In all experiments the blood pressure reduction was transient and the blood pressure increased immediately after termination of the infusion. The analogues were used both as esters and acids for the experiments.

The irritant effect of the prostaglandin analogues was tested using a behavioural model in cats. In this model the irritant effect on the eye is studied by registering the degree of eyelid closure and the behaviour of the animals. Compounds that cause discomfort and pain in the eye cause the animals to close their eyes. The analogues were applied as carboxylic acid esters, to enhance bioavailability, topically on the eye as a single dose at different dose levels. The animals were then followed for several hours at regular intervals. Each compound and dose was tested on a group of 3-6 cats. At least 3 days elapsed between two consecutive tests on the same animals. An arbitrary scale from 0 (absence of irritation) to 3 (marked irritation), with half steps was used.

The relaxant effect on the human penile cavernous tissue of PGE_1, and 19R-OH-PGE_2 are presented in Table I. It can be seen that PGE_1 and 19R-OH-PGE_2 were about equieffective and comparable to carbachol, however PGE_1 was slightly more potent than 19R-OH-PGE_2. Since 19R-OH-PGE_2 is a selective EP_2 receptor agonist this finding indicates that the EP_2 receptor accounts for most of the relaxant effect of PGE_1. Furthermore, in Fig.1 it is demonstrated that the concentration-response curves of PGE_1 and 19R-OH-PGE_2 are parallel and differ only with a factor of about 2-3, i.e. the latter analogue is about half to one third as potent as the former.

Table I. Relaxation of human corpus cavernosum tissue induced by prostaglandins compared to carbachol (10^{-6} M). (Mean±SEM)

Compound	n	Reduction in tension (%)	EC-50 (Moles/l)
Carbachol	8	100.0±0.0	--
PGE_1	8	90.9±3.7	2.5×10^{-7}
19R-OH-PGE_2	8	96.9±3.1	6.9×10^{-7}

The vasodilatory effect of PGE_1 and the EP_2 receptor agonist 19R-OH-PGE_2 on rabbit penile blood vessels is demonstrated in Fig 2. It can be seen that the two

prostaglandins had the same efficacy in inducing vasodilatation and were also about equipotent. This furthermore demonstrates that the EP_2 receptor mediates most of the vasodilatory effect of PGE_1. The vasodilatory effect of all the prostaglandin analogues as studied in the rat by investigating the immediate reduction in blood pressure upon intravenous infusion is presented in Table II. As can be seen in the table PGE_1 and the three hydroxy-substituted PGE_2 analogues effectively reduced the blood pressure in the anaesthetized rat, demonstrating an acute vasodilatory response.

Table II. Reduction of blood pressure in anaesthetized rats by prostaglandin analogues with agonistic effect on the EP_2 receptor. (n= 3 for each dose; Mean±SEM)

Prostaglandin analogue	2.5 - 3.5 µg/kg		7.5 - 10 µg/kg		25 - 35 µg/kg	
	Blood pressure o (mmHg)	Reduction (%)	Blood pressure o (mmHg)	Reduction (%)	Blood pressure o (mmHg)	Reduction (%)
PGE_1	114±20	13±4	105±15	35±5	103±9	52±3
18RS-OH-PGE_2	122±28	7±3	123±33	15±3	115±32	32±2
19R-OH-PGE_2	115±14	13±10	103±12	31±3	91±9	43±6
20-OH-PGE_2	91±11	26±5	85±10	38±3	91±6	44±0

Blood pressure o = blood pressure before infusion of prostaglandin analogue.

The irritant effects of the three prostaglandin analogues and PGE_1 as studied in the feline eye are presented in Table III. All three hydroxy-substituted PGE_2-analogues had significantly less irritant effect than PGE_1-isopropyl ester and PGE_1 acid. Most surprisingly we found that both 18RS-OH-PGE_2-methyl ester and 19R-OH-PGE_2-methyl ester had no or markedly reduced irritant effect, even at doses 1000 times higher than PGE_1-isopropyl ester. Previously it has been shown that 19R-OH-PGE_2 does not cause lid closure in rabbits but induces an irritant effect by inducing swelling of the ocular structures (Hall and Jaitly, 1977). We found no evidence of such irritation in the cat eye with 19R-OH-PGE_2 or the other hydroxy-substituted PGE_2 analogues.

To confirm that 19R-OH-PGE_2-methyl ester, which is more hydrophilic than PGE_1-isopropyl ester, indeed penetrates into the cornea and the intraocular parts of the eye we measured the intraocular pressure in 3 cats under local anaesthesia before and 1

hour after topical administration of the prostaglandin to the eye. The intraocular pressure was measured by pneumatonometry. One eye was treated with the test compound and the other eye received the vehicle only. In the eyes treated topically with 19R-OH-PGE_2-methyl ester the intraocular pressure decreased from 16.3 +/- 0.9 mmHg to 12.7+/-1.2 mmHg, whereas it was 16.3+/-0.9 mmHg and 15.7+/-0.7 mmHg in the control eyes at the same time points. It is well known that prostaglandins reduce the intraocular pressure in cats (Bito et al., 1989), and it can thus be taken as an evidence that the drug has penetrated into the eye. Furthermore, from Table III it can also be seen that the PGE_1 acid, which is a much less lipophilic compound than the 18-, 19- and 20-hydroxy-substituted PGE_2-methyl ester analogues, caused significantly more irritation, and at much lower dose, than the hydroxy-substituted analogues. Thus the absence of pain and irritation after administration of 18RS-OH-PGE_2, 19R-OH-PGE_2 and 20-OH-PGE_2 cannot be explained on the basis of increased hydrophilicity and poor bioavailability. Accordingly, selective EP_2 prostanoid receptor agonists seem to be very advantageous in that they exhibit no, or markedly reduced irritant effect.

Table III. Maximum irritative effect of prostaglandin analogues as studied in cat eyes. The log P values were estimated based on thin layer chromatography with $PGF_{2\alpha}$ isopropyl ester as reference (log P 4.5). ie= isopropyl ester, me= methyl ester. Maximum irritation =3. Mean±SEM (n= 3-6).

Analogue	log p-value	Dose: 0.01 µg	Dose: 0.1 µg	Dose: 0.3 µg	Dose: 1 µg	Dose: 3 µg	Dose: 10 µg	Dose: 30 µg	Dose: 100 µg
PGE_1-ie	4.7	0.4±0.2	1.7±0.3	2.8±0.1	-	-	-	-	-
PGE_1 acid	0.7	-	0.6±0.1	-	1.6±0.2	-	3.0±0.0	-	-
18RS-OH-PGE_2-me	2.7	-	-	-	0.0±0.0	0.0±0.0	0.0±0.0	0.3±0.2	-
19R-OH-PGE_2-me	2.5	-	0.0±0.0	-	0.1±0.1	-	0.1±0.1	-	0.7±0.4
20-OH-PGE_2-me	2.2	-	-	-	-	0.5±0.0	1.2±0.2	1.2±04	-

References

Anawalt, B.D., Bebb, R.A. and Matsumoto, A.M. 1996. Medical therapy for erectile dysfunction. Current Opinion in Endocrinology and Diabetes. 3; 472-477.

Bito, L.Z., Camras, C.B., Gum, G.G. et al. 1989. The ocular hypotensive effect and side-effects of prostaglandins on the eyes of experimental animals. In: The ocular effects of prostaglandins and other eicosanoids (Eds: L.Z. Bito and J. Stjernschantz). Alan R. Liss Inc. New York. pp:349-368.

Coleman, R.A., Smith, W.L. and Narumiya, S. 1994. VIII. International Union of Pharmacology classification of prostanoid receptors: Properties, distribution, and structure of the receptors and their subtypes. Pharmacological Reviews. 46; 205-229.

Hall, D.W.R. and Jaitly, K.D. 1977. Inflammatory responses of the rabbit eye to prostaglandins. Agents-Actions-Suppl. 2: 123-133.

NIH Consensus Conference on Impotence. 1993. JAMA. 270;83-90.

Pada-Nathan, H., Hellstrom, W.G.J., Kaiser, F.E. et al. 1997. Treatment of men with erectile dysfunction with transurethral alprostadil. New Eng. J. Med. 336;1-7.

Taylor, P.L. and Kelly R.W. 1974. 19-hydroxylated E prostaglandins of human semen. Nature. 250; 665-667.

Wolfson, B., Pickett, S., Scott, N.E. et al. 1993. Intraurethral prostaglandin E-2 cream: A possible alternative treatment for erectile dysfunction. Urology. 42; 73-75.

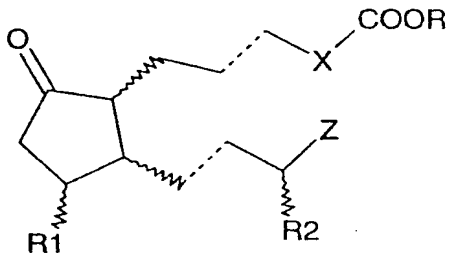
Claims:

1. A composition for the treatment of impotence or erectile dysfunction, comprising a therapeutically active and physiologically acceptable amount of a prostaglandin, wherein the prostaglandin is a selective EP_2 or EP_4 receptor agonist, or an active derivative including a salt or an ester thereof.

2. The composition according to claim 1, wherein , the prostaglandin is a selective EP_2 receptor agonist, or an active derivative including a salt or an ester thereof.

3. The composition according to claim 1, wherein the prostaglandin is of the E-type including a salt or an ester thereof.

4. The composition according claim 1, 2 or 3, wherein the prostaglandin is a compound of the general formula:



wherein:

R is hydrogen, a salt moiety (e.g. alkali or ammonium), a straight or branched, saturated or unsaturated alkyl chain, preferably with 1-10 carbon atoms, an alicyclic ring, preferably with 3-8 carbons, arylalkyl, preferably aryl-C2-5 alkyl, or an aryl ring;

X is a straight saturated or unsaturated alkyl chain, preferably containing 2-5 carbon atoms, optionally interrupted by a heteroatom, selected from oxygen, nitrogen and sulfur, and optionally containing a cycloalkyl, , aryl or a heteroaryl group,

R1 and R2, which are identical or different, are hydrogen, hydroxy, halogen, oxygen (keto or alkoxy) or an alkyl group with 1-3 carbons or an ester OCOR3, where R3 is a straight or branched, saturated or unsaturated alkyl group, preferably containing 1-10, especially 1-6 carbons, or a cycloalkyl, preferably containing 3-7 carbons, or an arylalkyl group, esp. aryl C2-5 alkyl (e.g. benzyl);

Z is an alkyl chain of 1-8 carbons, saturated or unsaturated, optionally interrupted by one or more heteroatoms (O, N, S), straight or branched containing alkyl substituents, or containing an alicyclic ring or an aryl or heteroaryl ring,

and containing one or more, preferably one substituent Y, selected from hydroxy, oxygen (keto), hydroxy, sulfhydryl, amino, methylamino, dimethylamino, and C_{1-3} alkoxy,

5. The composition according to any one of claims 1 to 4, wherein the prostaglandin is 19-OH-PGE_2, or a salt or an ester thereof.

6. The composition according to claim 5, wherein the prostaglandin is 19R-OH-PGE_2, or a salt or an ester thereof.

7. The composition according to claim 6, wherein the prostaglandin is 19R-OH-PGE_2-methyl or isopropyl ester.

8. The composition according to claims 1-4, wherein the prostaglandin is 18-OH-PGE_2 or a salt or an ester thereof.

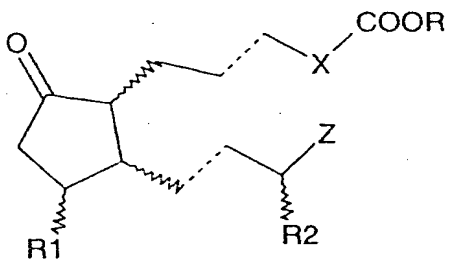
9. The composition according to claims 1-4, wherein the prostaglandin is 20-OH-PGE_2 or a salt or an ester thereof.

10. A method of treating impotence or erectile dysfunction, which comprises administering to a human a therapeutically effective and physiologically acceptable amount of a prostaglandin which is a selective EP_2 or EP_4 receptor agonist, or a derivative including a salt and an ester thereof.

11. The method according to claim 10, wherein the prostaglandin is a selective EP_2 receptor agonist.

12. The method according to claim 10 or 11, wherein the prostaglandin is of the E-type, including a salt and an ester thereof.

13. The method according to claims 10, 11 or 12, wherein the prostaglandin is a compound of the general formula:



wherein:
R is hydrogen, a salt moiety, a straight or branched, saturated or unsaturated alkyl chain, preferably with 1-10 carbon atoms, an alicyclic ring, preferably with 3-8 carbons, arylalkyl, preferably aryl-C2-5 alkyl, or an aryl ring;

X is a straight saturated or unsaturated alkyl chain, preferably containing 2-5 carbon atoms, optionally interrupted by a heteroatom, selected from oxygen, nitrogen and sulfur, and optionally containing a cycloalkyl, , aryl or a heteroaryl group,

R1 and R2, which are identical or different, are hydrogen, hydroxy, halogen, oxygen (keto or alkoxy) or an alkyl group with 1-3 carbons or an ester OCOR3, where R3 is a straight or branched, saturated or unsaturated alkyl group, preferably containing 1-10, especially 1-6 carbons, or a cycloalkyl, preferably containing 3-7 carbons, or an arylalkyl group, esp. aryl C2-5 alkyl (e.g. benzyl);

Z is an alkyl chain of 1-8 carbons, saturated or unsaturated, optionally interrupted by one or more heteroatoms (O, N, S), straight or branched containing alkyl substituents and/or and containing an alicyclic ring or an aryl or heteroaryl ring,

and containing one or more, preferably one substituent Y, selected from hydroxy, oxygen (keto) , hydroxy, sulfhydryl, amino, methylamino, dimethylamino, and C_{1-3} alkoxy,

14. The method according to any one of claims 10-13, wherein the prostaglandin is 19-OH-PGE_2, or a salt or an ester thereof.

15. The method according to claim 14, wherein the prostaglandin is 19R-OH-PGE_2, or a salt or an ester thereof.

16. The method according to claim 15, wherein the prostaglandin is 19R-OH-PGE_2-methyl or isopropyl ester.

17. The method according to claims 10-13, wherein the prostaglandin is 18-OH-PGE_2, or a salt or an ester thereof.

18. The method according to claims 10-13, wherein the prostaglandin is 20-OH-PGE_2, or a salt or an ester thereof.

19. The method according to any one of clams 8-14, wherein the prostaglandin is administered by intracavernous injection, or by transurethral or transdermal application, including on the glans of the penis.

20. Use of a prostaglandin which is a selective EP_2 or EP_4 receptor agonist, or an active derivative including a salt or an ester thereof, as defined in any one of claims 1 to 9 for the preparation of a medicament for treatment of impotence or erectile dysfunction.

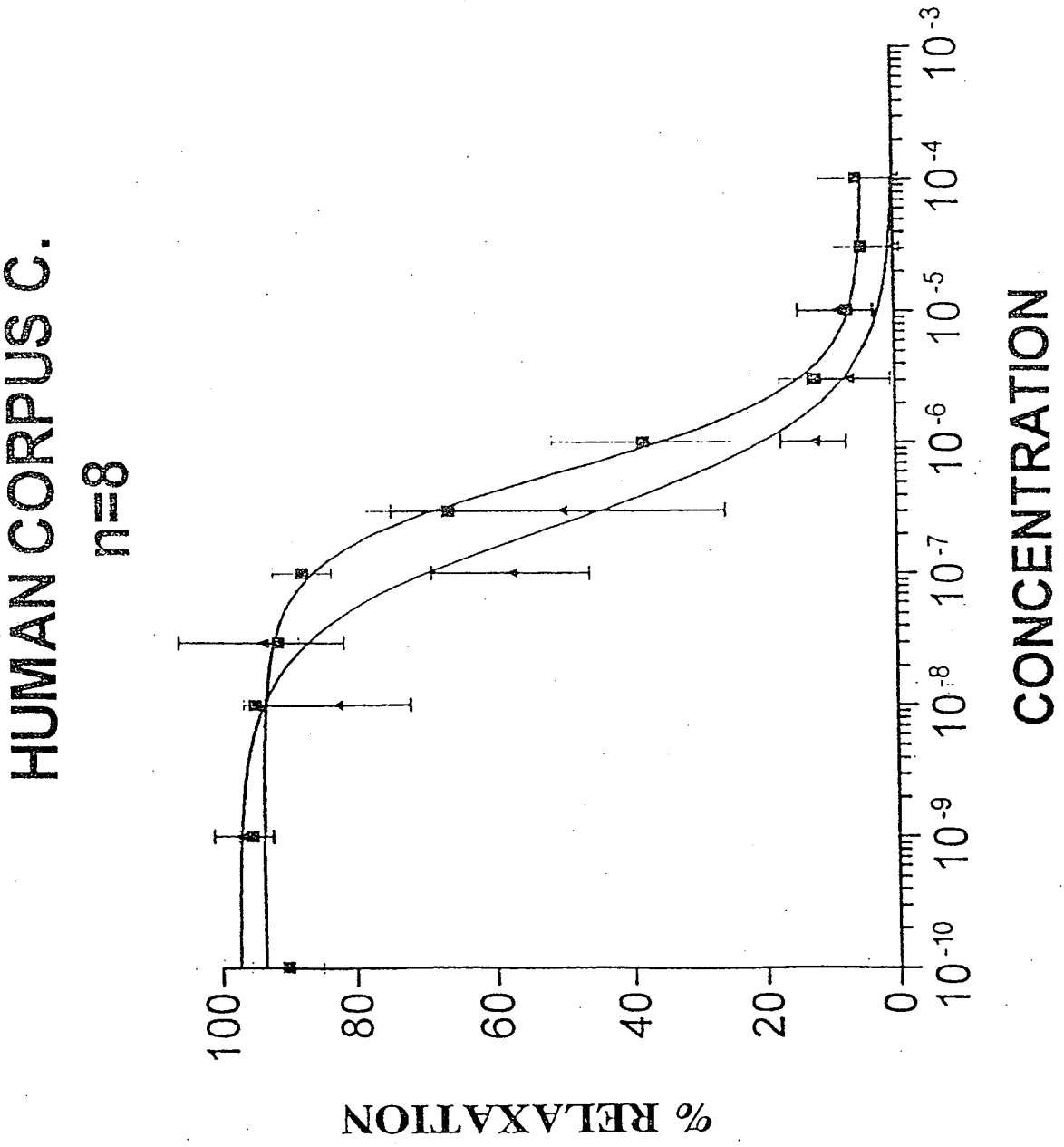

19R-HYDROXY-PGE
PGE1
HUMAN CORPUS C.
n=8
% RELAXATION
100
80
60
40
20
0
10-10
10-9
10-8
10-7
10-6
10-5
10-4
10-3
CONCENTRATION

FIG. 1

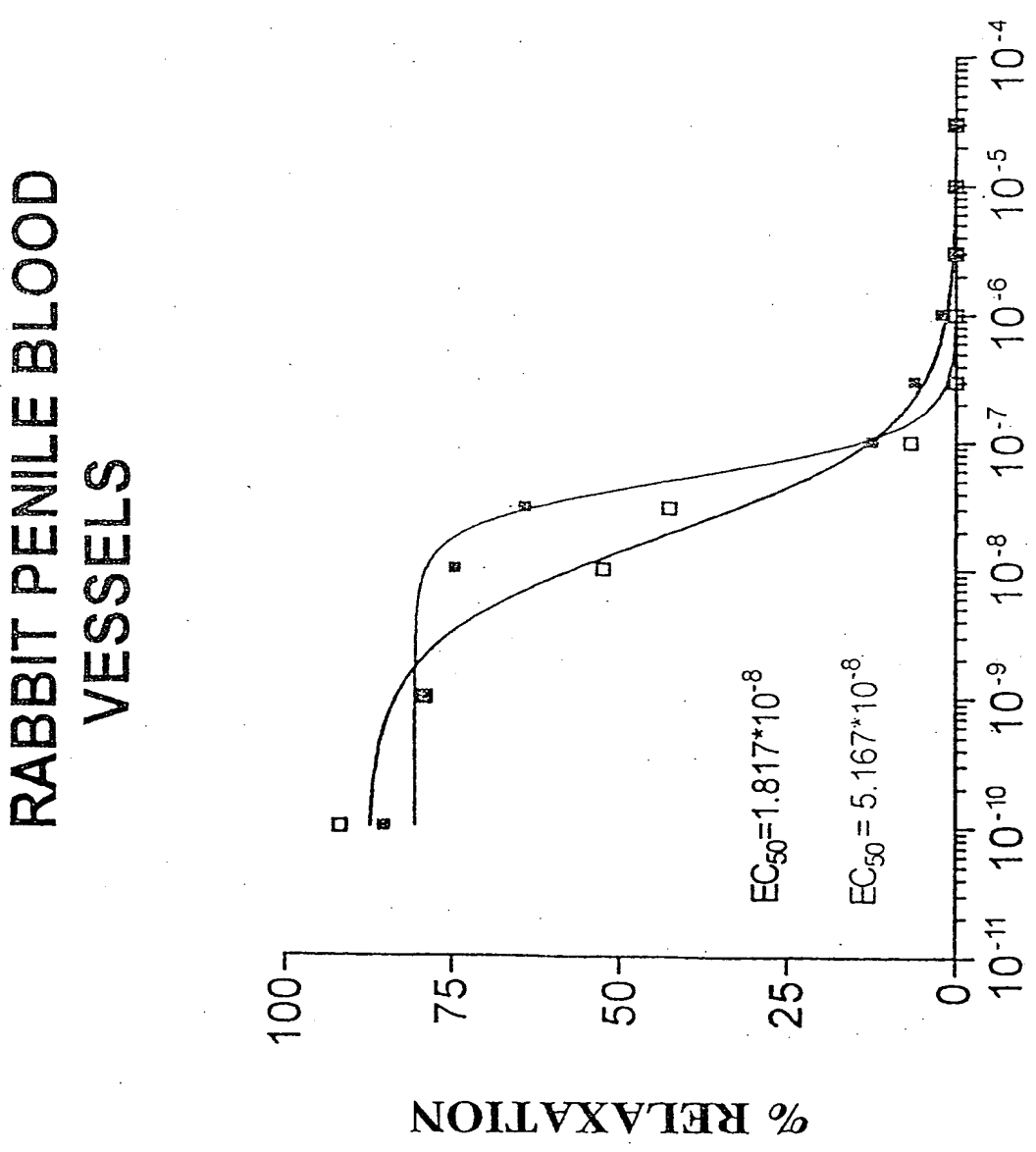

RABBIT PENILE BLOOD VESSELS
19R-HYDROXY-PGE2
PGE1
% RELAXATION
CONCENTRATION
100
75
50
25
0
10-11
10-10
10-9
10-8
10-7
10-6
10-5
10-4
EC50=1.817*10-8
EC50 = 5.167*10-8

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01367

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/557
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9300894 A1 (SCOTT, NATHAN, E.), 21 January 1993 (21.01.93)	1-3,20
X	WO 9632141 A1 (SAM YANG CO., LTD.), 17 October 1996 (17.10.96)	1-3,20
A	British Journal of Pharmacology, Volume 116, 1995, Roma A, Armstrong, "Investigation of the inhibitory effects of PGE2 and selective EP agonists on chemotaxis of human neutrophils" page 2903 - page 2908	20

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1998	01 -11- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01367

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Biochemistry, Volume 35, 1996, Li Zeng et al, "Selective Regulation of RNK-16 Cell Matrix Metalloproteinases by the EP4 Subtype of Prostaglandin E2 Receptor" page 7159 - page 7164 --	20
X	US 4190670 A (ARTHUR F. MARX ET AL), 26 February 1980 (26.02.80), tables 2 and 3 --	1-6,8,9
X	Chemical Abstracts, Volume 87, No 7, 15 August 1987 (15.08.87), (Columbus, Ohio, USA), Spilman, C. H., "Effects of 19-hydroxyprostaglandins on oviductal and uterine motility", page 58, THE ABSTRACT No 48352q, Prostaglandins 1977, 13 (4), 795-805 --	1-7
X	Chemical Abstracts, Volume 120, No 1, 3 January 1994 (03.01.94), (Columbus, Ohio, USA), Woodward, D.F. et al, "Identification of 19(R)-OH prostaglandin E2 as a selective prostanoid EP2-receptor agonist", page 161, THE ABSTRACT No 1279f, Prostaglandins 1993, 46 (4), 371-383 -- --------	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01367

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-19
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [X] Claims Nos.: 20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The expression "selective EP2 or EP4 receptor agonist" in claim 20 is indefinite. According to PCT Article 6, the claims shall be clear and concise. Claim 20 has therefore not been fully searched.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/01367

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9300894 A1	21/01/93	AU 2300092 A	11/02/93
		US 5708031 A	13/01/98
WO 9632141 A1	17/10/96	CN 1181022 A	06/05/98
		EP 0831942 A	01/04/98
		US 5653352 A	05/08/97
		US 5741511 A	21/04/98
US 4190670 A	26/02/80	AU 497219 B	07/12/78
		AU 7949875 A	30/09/76
		BE 827156 A	25/09/75
		CH 615159 A	15/01/80
		DE 2513222 A	02/10/75
		DK 125975 A	27/09/75
		FR 2265361 A,B	24/10/75
		GB 1501864 A	22/02/78
		JP 50135283 A	27/10/75
		LU 72128 A	20/08/75
		NL 7503654 A	30/09/75
		SE 7503438 A	29/09/75
		US RE30287 E	27/05/80
		US 4054595 A	18/10/77
		US 4164446 A	14/08/79
		ZA 7501882 A	31/03/76